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| 09/810,310 | 03/14/2001 | Samir Khleif | 15280415100 | 9099 |

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| EXAMINER | |
|---|---|
| DIBRINO, MARIANNE NMN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/810,310 | KHLEIF ET AL. | |
| | Examiner | Art Unit | |
| | DiBrino Marianne | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,6-8,11,12 and 14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-8, 11, 12, 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/17/07 has been entered.

The Declaration of Dr. Jay Berzofsky under 37 CFR 1.132 filed on 10/17/07 is acknowledged and has been entered.

Claims 1, 2, 6-8, 11, 12 and 14-17 are presently being examined.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 2, 6, 11, 12 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Corr *et al* (J. Exp. Med. 1996, 184: 1555-1560, of record) in view of Corr *et al* (J. Immunol. 1997, 159: 49999-5004, of record).

Corr *et al* (1996) teach IM injection of a naked plasmid DNA encoding a viral protein antigen, said antigen comprising one or more T cell epitopes. Corr *et al* (1996) teach that muscle cells at the site of injection do not present antigen to the immune system, but rather professional bone marrow-derived APCs present the antigen that results in a CTL response to said antigen. Corr *et al* further teach that antigen presentation and co-stimulation do not need to be provided by the same cell but must be in the same local environment (see entire reference).

Corr *et al* (1996) do not teach wherein an antigen-specific CTL response is elicited in a subject by administering a peptide or protein antigen comprising one or more T cell epitopes, including those recited in the instant dependent claims, coordinately with a non-viral vector, including those recited in the instant dependent claims, comprising a polynucleotide encoding at least one of a B7-1, -2 or -3 co-stimulatory molecule separately to closely adjacent sites.

Corr *et al* (1997) teach "we injected mice intradermally or i.m. with plasmid DNA encoding a MHC class I-restricted peptide Ag (minigene) and different membrane-bound costimulatory ligands. The minigene-encoded epitope only primed a specific CTL response if injected in the vicinity of an ectopically expressed costimulatory

ligand...These results show that functional B7-1 transfection can be achieved in vivo and induces the selective induction of CTL." (especially abstract). Corr *et al* (1997) teach that co-expression of B7-1 in the vicinity of a minimal MHC class I-restricted antigen is sufficient to prime a CTL response. Corr *et al* (1997) further teach IM or intradermal injection of protein antigen mixed with plasmid DNA encoding B7.1 or B7.2 co-stimulatory molecule. Corr *et al* (1997) teach that expression of the MHC class I restricted epitope in the same cell as the costimulatory ligand is not imperative for T cell priming, but *in vivo* a T cell cannot be effectively primed with a cognate signal from a peripheral somatic tissue if a second signal stimulus is not available in the immediate vicinity, for example in the same muscle. Corr *et al* (1997) teach that *in vivo* transfection of peripheral somatic tissues with plasmids encoding costimulatory ligands not only enhanced immune responses to antigen expressed by gene vaccination, but also dramatically increased the immune response to coinjected protein antigens. Corr *et al* (1997) teach that by increasing the density of membrane-bound costimulatory molecules, naked plasmid DNA injection can boost immune responses to soluble protein antigen in a manner analogous to conventional adjuvants, but without apparent systemic side effects. Corr *et al* (1997) teach that the plasmid DNA were constructed with a promoter regulatory element for high expression (especially page 5001 at column 2, page 5001 at columns 1 and 2, page 5003).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered a viral protein antigen such as one taught by Corr *et al* (1996) or the CTL peptide epitope taught by Corr *et al* (1997) separately from the naked plasmid DNA encoding B7.1 and/or B7.2 co-stimulatory molecule to closely adjacent sites.

One of ordinary skill in the art would have been motivated to do this because co-administration or separate administration to closely adjacent sites are equivalent methods, and for convenience and standardization between administrations, because the same naked plasmid DNA preparation administered separately to a closely adjacent site could be used for co-ordinate immunizations with different protein or peptide antigens, and because Corr *et al* (1997) teach that co-expression of B7-1 in the vicinity of a minimal MHC class I-restricted antigen is sufficient to prime a CTL response, including wherein the antigen is a protein antigen.

Claim 14 is included in this rejection because the peptide antigen administered separately to a closely adjacent site is "administered to the subject in a sequential vaccination protocol." Alternatively, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered to the subject in a sequential vaccination protocol to establish ectopic expression of the costimulatory molecule(s) prior to protein or peptide antigen administration since both Corr references teach antigen presentation and co-stimulation do not need to be provided by the same cell but must be in the same local environment.

Applicant's arguments, of record in Applicant's response filed 10/17/07 (on pages 4-8), have been fully considered but are not persuasive.

Briefly, Applicant argues that the references do not render the claims prima facie obvious because the references do not teach or suggest separate administration to closely adjacent sites, nor do they provide a sufficient motivation to achieve this limitation as recited in the claims: (1) Corr (1996) does not teach IM injection of a viral protein antigen mixed with naked plasmid DNA encoding a viral protein, (2) Applicant disagrees with the Examiner's interpretation of Corr (1997), such as for example that the discussion presented by Corr (1997) to co-expression of B7-1 in the vicinity of a minimal MHC class I-restricted antigen is sufficient to prime a CTL response does not relate to the administration of a plasmid expression B7-1 in combination with a soluble antigen, (3) Corr (1997) show in Fig.4 on page 5002 that enhancement of a CTL or antibody response depended on the presence of the costimulatory plasmid mixed together with the antigen-encoding plasmid and administered together at the same site, not administered separately at adjacent sites, (4) Corr (1977) demonstrate an antibody response only when protein antigen and B7-encoding DNA are co-administered as a mixture and injected at the same site (Fig. 5 on page 5001 and right column at lines 31-35), (5) the experiment in which protein antigen is mixed with DNA plasmid encoding B7-1 (Fig. 5) demonstrates only an antibody response, not a CTL response, (6) Corr (1997) clearly discloses that the administration of a naked plasmid encoding a co-stimulatory B7 molecule together with a plasmid encoding an antigen or an epitope of an antigen is not the same as injecting the costimulatory plasmid together with the protein antigen as in the former instance a CTL response is induced and in the latter an antibody response is induced, (7) in both cases the immune response was only induced when the two plasmids or the plasmid encoding a costimulatory molecule and the polypeptide were injected mixed together at the same site.

It is the Examiner's position in response to Applicant's argument that: (1) The Examiner agrees that Corr *et al* (1996) do not teach IM injection of a viral protein antigen mixed with naked plasmid DNA encoding a viral protein, (2) Although Corr *et al* (1997) do not exemplify administration of a plasmid expression B7-1 in combination with a soluble antigen producing a CTL response, they teach that co-expression of B7-1 in the vicinity of a minimal MHC class I-restricted antigen is sufficient to prime a CTL response, (3) Corr *et al* (1997) demonstrate enhancement of an immune response when the plasmid encoding a costimulatory molecule was mixed together with an antigen-encoding plasmid and administered together at the same site, (4) Corr *et al* (1997) demonstrate an antibody response when protein antigen and B7-encoding DNA are co-administered as a mixture and injected at the same site, but not when each one is separately administered to non-related sites, (5) Corr (1997) did not test for a CTL response using B7-encoding DNA and protein or peptide antigen, (6) and (7) Corr (1997) do *not* disclose that the administration of a naked plasmid encoding a co-stimulatory B7

molecule together with a plasmid encoding an antigen or an epitope of an antigen is not the same as injecting the costimulatory plasmid together with the protein antigen as in the former instance a CTL response is induced and in the latter an antibody response is induced because in both instances the plasmids or the plasmid and the protein or peptide antigens were administered separately to non-related sites when no immune response was produced, and in the former instance (administration of two plasmids) both a CTL and an antibody response were induced and in the latter instance (administration of a plasmid and a protein or peptide antigen) the authors only tested for an antibody response.

It is the Examiner's further position that although Corr exemplifies coadministration, Corr teaches that the second signal only be available in the immediate vicinity of the MHC class I restricted epitope, such as for example, in the same muscle and that it is not imperative for T cell priming that expression of the MHC class I restricted epitope be in the same cell as the costimulatory ligand.

With regard to the arguments presented in the Declaration of Dr. Jay Berzofsky under 37 CFR 1.132 filed 10/17/07 that are not duplicated in the arguments presented on pages 4-8 of the said response: at items #9 and #12, Applicant is arguing the reference separately.

For the reasons enunciated herein, it is the Examiner's position that one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of the references to produce the invention as claimed with a reasonable expectation of success.

4. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Corr *et al* (J. Exp. Med. 1996, 184: 1555-1560 of record) in view of Corr *et al* (J. Immunol. 1997, 159: 49999-5004 of record) as applied to claims 1, 2, 6, 11, 12 and 14-17 above, and further in view of WO 99/45954 A1 (of record).

Corr *et al* (1996) and Corr *et al* (1997) have been discussed supra, hereafter referred to as "the combined references." The combined references do not teach wherein the viral antigen is from HBV, HCV, HSV or HPV.

WO 99/45954 A1 teaches that epitopes on antigens such as HBV, HCV, HPV and HSV are useful in pharmaceutical compositions for both therapeutic and diagnostic applications. WO 99/45954 A1 further teaches that the peptides bind to class I HLA molecules, i.e., are about 8-11 amino acid residues in length (especially paragraph spanning pages 2-3, first full paragraph on page 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the epitopes or protein antigens taught by WO 99/45954 A1 in the method taught by the combined references.

One of ordinary skill in the art would have been motivated to do this because the combined references teach an improved method for generating an effective immune response, and WO 99/45954 A1 teaches that epitopes on antigens such as HBV, HCV, HPV and HSV are useful in pharmaceutical compositions for both therapeutic and diagnostic applications.

Applicant's arguments, of record in Applicant's response filed 10/17/07 (on pages 4-8), have been fully considered but are not persuasive.

Applicant's arguments to the prior rejection at item #3 of this Action apply herein, and thus Examiner's comments on Applicant's arguments at item #3 of this Action also apply herein.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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December 27, 2007

12/28/07

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER